SULFUR DIOXIDE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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A. Abstract

Sulfur dioxide is an irritant gas commonly emitted by coal fired power plants, refineries, smelters, paper and pulp mills and food processing plants. Both controlled laboratory studies and epidemiology studies have shown that people with asthma and children are particularly sensitive to and are at increased risk from the effects of SO_2 air pollution. Asthmatic subjects exposed to levels of SO_2 within regulatory standards have demonstrated increased respiratory symptoms such as shortness of breath, coughing and wheezing, and decrements in lung function. Physiological differences between children and adults such as lung volume and ventilation rate make children more sensitive to the effects of SO_2 compared to healthy adults. In general, children's exposure to SO_2 is also greater than that of adults since they spend more time outdoors and are more physically active.

Controlled exposures to SO_2 have shown statistically significant reductions in lung function at concentrations as low as 0.1 to 0.25 ppm. Epidemiologic studies have seen mortality associated with very small increases in ambient SO2 in the range of 10 – 22 ppb. Low birth weigh is associated with SO2 concentrations in the range of 22-40 ppb. The studies assessed in this review indicate that infants and people with asthma are particularly susceptible to the effects of SO_2, even at concentrations and durations below the current California one-our standard of 0.250 ppm.

B. Background

Sulfur dioxide (SO_2) is a water soluble, irritant gas commonly emitted into ambient air by coal fired power plants, refineries, smelters, paper and pulp mills, and food processing plants. Adverse health effects from SO_2 exposure at ambient concentrations have mainly been seen in individuals with asthma as will be summarized in this review. SO_2 exposure causes bronchoconstriction, decrements in respiratory function, airway inflammation, and mucus secretion. There is some epidemiologic evidence of a population effect from SO_2 exposure in sensitive sub-populations as listed below. However, the effects of SO_2 alone are very difficult to determine because SO_2 is often associated with PM and other pollutants. Currently, there are two standards set by California for SO_2: a one hour standard of 0.25 ppm and a 24 hr standard of 0.04 ppm..

SO_2 is also a precursor of secondary sulfates such as sulfuric acid, which is a stronger irritant than SO_2, and plays a major role in the adverse respiratory effects of air pollution. Sulfate is a major component of $PM_{2.5,}$ which has been implicated in causing adverse health effects, especially among the elderly and persons with cardiovascular and respiratory illnesses (Koenig, 1997). This review will summarize the health effects of SO_2 and some of the findings from both controlled laboratory and epidemiologic studies that are relevant to human health.

C. Principal sources and exposure assessment

C.1. Relationship between SO_2 and sulfuric acid

Since SO_2 is a water soluble and reactive gas, it does not remain long in the atmosphere as a gas. Much of the SO_2 emitted is transformed through oxidation into acid aerosols, either sulfuric acid (H_2SO_4) or partially neutralized H_2SO_4 [ammonium bisulfate or ammonium sulfate]. The ecological effects of acid aerosols (in the form of acid rain or dry deposition) have received much attention but are not the subject of this report.

C.2. Assessment of Response

Various lung measurements have been used to assess the response to inhaled SO_2 in controlled laboratory studies. Two of the most widely used tests of lung function are FEV_1 and SRaw.

FEV_1 is the volume of air exhaled in the first second of a forced expiratory maneuver. This is the most reproducible measure of acute changes in airway caliber. Stimuli that reduce airway caliber such as pollen exposure, methacholine challenges and cigarette smoke can all reduce a subject's FEV_1. Changes in FEV_1 have been widely used to assess the health effects of ambient air pollutants. SO_2, ozone, sulfuric acid, and nitrogen dioxide exposures are associated with reduced FEV_1.

Specific airway resistance (SRaw) is another sensitive measurement of airway caliber. Airway resistance is usually measured using a plethysmograph. Specific airway resistance is adjusted for a specific lung volume, often measured as thoracic gas volumes.

Provocative challenges, such as the methacholine challenge, are performed to document individual bronchial hyperresponsiveness (BHR). In the methacholine challenge test, subjects are asked to inhale increasing concentrations of methacholine (usually from 0 to 25 mg/ml) until the FEV_1 measured post inhalation drops by 20%. The results of the challenge are presented as the provocative concentration (PC) necessary to cause a 20% decrease (PC_{20}) in FEV_1.

Bronchoalveolar and nasal lavage (BAL or NL) are two techniques that provide the investigator with cells and fluids for biochemical assays. Either the airways or the nose is washed with sterile saline and the fluid collected for analysis. The elevation of cytokines, cells or inflammatory mediators are indicators of adverse effects. BAL fluid often contains alveloar macrophages, neutrophils, and eosinophils.

Respiratory symptoms such as shortness of breath, coughing, wheezing, sputum production, and medication use are also commonly used to assess the effects of air pollution exposure. Subjects are given diary forms which they complete daily for the duration of the study.

D. Description of Key Studies

D.1. Controlled Studies

Since individuals with asthma are much more sensitive to the respiratory effects of inhaled SO_2, the review of controlled laboratory studies is restricted to studies of subjects with asthma. This follows a similar decision made by the US EPA in its supplement to the second addendum to Air Quality Criteria for PM and Sulfur Oxides (EPA, 1994). As noted in the EPA document, air temperature and humidity and exercise alone can affect respiratory function in subjects with asthma. Thus, these variables need to be considered in the review as well as individual susceptibilities among those with asthma.

EPA reviewed the status of controlled exposures to SO_2 in the second addendum to Air Quality Criteria for PM and Sulfur Oxides (EPA, 1994). This report will touch on that literature briefly and concentrate on studies subsequent to 1993.

Prior to 1980 controlled exposures of human subjects to SO_2 had involved only healthy subjects. In general these studies did not find adverse respiratory effects even at concentrations of 13 ppm (Frank et al, 1962). In 1980 and 1981, Koenig et al (1980; 1981) and Sheppard et al (1980; 1981) published the results of controlled SO_2 exposures in both adolescent and adult subjects with asthma.

The studies by Koenig and Sheppard found that people with asthma were extremely sensitive to inhaled SO_2 and therefore may be at increased risk for adverse respiratory effects in communities where SO_2 concentrations are elevated even for short periods of time. A series of studies with adolescents showed gradations in SO_2 effects dependent on whether subjects had allergic vs non-allergic asthma and whether they had exercise-induced bronchoconstriction.

This gradation of response in FEV_1 after SO_2 exposure is shown in Figure 1. The changes after SO_2 exposure were statistically significant. No significant changes were seen after exposure to air. Similar studies with healthy subjects often do not find significant pulmonary function decrements after exposure to 5.0 ppm SO_2 (Koenig, 1997).

Figure 1: FEV_1 changes after SO2 exposure

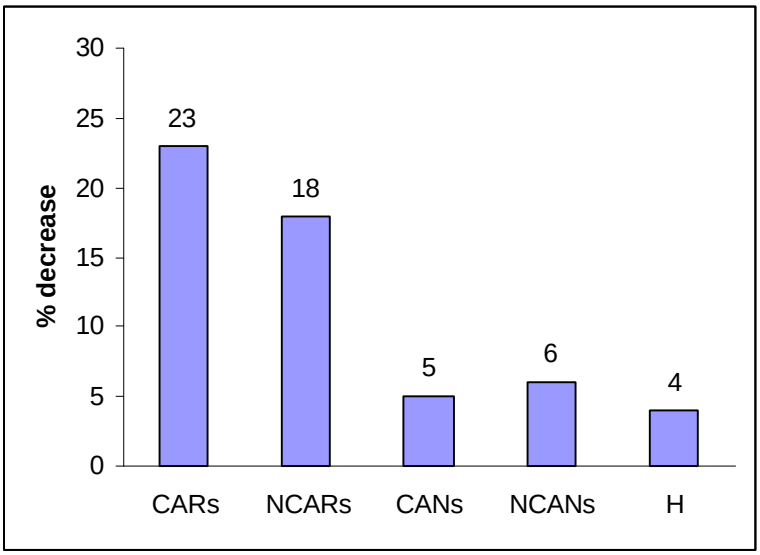

Figure 1. Average decrements in FEV_1 after exposure to 1.0 ppm SO_2 during intermittent moderate exercise. CAR- physician diagnosed, allergic asthmatic responder; NCAR- non physician diagnosed, allergic asthmatic responder; CANs- physician diagnosed, allergic non-asthmatics; NCANs- non physician diagnosed, allergic non-asthmatics; H- healthy.

Table 1. Percentage change in pulmonary function measurements after exposure to 1.0 ppm SO_2 or air in nine adolescent asthmatic subjects.

Measurement	Change from baseline	
	SO_2 exposure	Air exposure
FEV_1	23% decrease	0% change
R_T	67% increase	13% decrease
V_{max50}	44% decrease	9 % increase
V_{max75}	50% decrease	24% increase

From Koenig et al, 1981

Pulmonary function is dramatically decreased in asthmatics exposed to SO_2 as shown in Table 1 and in Figure 1. Regarding the duration of exposure necessary to elicit a SO2 effect, Horstman and Folinsbeel (1986) demonstrated that SO_2 exposure for 2.5 minutes produced a significant decrement in pulmonary function tests (PFTs). In a recent study, Trenga et al (1999) found an average 2.4% decrement in FEV_1 when adult subjects were exposed to only 0.1 ppm SO_2 via a mouthpiece. As discussed below this route of exposure may exaggerate the SO_2 response.

D.1.1. Route of exposure. SO_2 is a highly water soluble gas and is rapidly taken up in the nasal passages during normal, quiet breathing. Studies in human volunteers found that, after inhalation at rest of an average of 16 ppm SO_2, less than 1% of the gas could be detected at the oropharynx (Speizer and Frank, 1966). Penetration to the lungs is greater during mouth breathing than nose breathing. Penetration also is greater with increased ventilation such as during exercise. Since individuals with allergic rhinitis and asthma often experience nasal congestion, mouth breathing is practiced at a greater frequency in these individuals (Ung et al, 1990) perhaps making them more vulnerable to the effects of water soluble gasses such as SO2. A number of more recent studies have shown that the degree of SO_2-induced bronchoconstriction is less after nasal inhalation than after oral inhalation (Kirkpatrick et al, 1982; Bethel et al., 1983; Linn et al, 1983; Koenig et al, 1985). Inhalation of SO_2 causes such dramatic bronchoconstriction that it appears little of the gas actually reaches the bronchial airways. However, nasal uptake of SO_2 does produce adverse consequences for the upper respiratory system, such as nasal congestion and inflammation. Koenig and co-workers (1985) reported significant increases in the nasal work of breathing (measured by posterior rhinomanometry) in adolescent subjects with asthma. Increases in airflow rate such as resulting from exercise can increase penetration to the lung (Costa and Amdur, 1996), therefore people exercising in areas contaminated with SO_2 may suffer exacerbated effects.

D.1.2. Duration of exposure. In early studies, large changes in pulmonary function were seen after only 10 minutes of moderate exercise during SO_2 exposure. Two contrasting effects of duration with SO_2 exposure have been documented. Short durations are sufficient to produce a response and longer durations do not produce greater effects. One study showed that as little as two minutes of SO_2 inhalation (1 ppm) during exercise caused significant bronchoconstriction, as measured by airway resistance. In addition, the study showed that the increase in airway resistance after 10 minutes of exposure to 1 ppm SO_2 during exercise was not significantly increased when the exposure was extended to 30 minutes (Horstman and Folinsbee, 1986).

D.1.3. Concentration-exposure relationships. EPA in their summary of the effects of SO_2 (1986) constructed a figure representing the distribution of individual airway sensitivity to SO_2 by using the metric of doubling of SRaw. Figure 2 clearly illustrates the exposure-response relationship of SO_2.

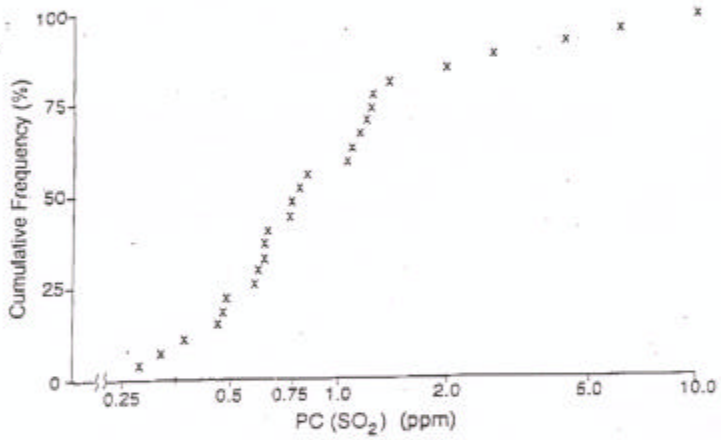

Figure 2. Distribution of individual airway sensitivity to SO_2, ($PC[SO_2]$). $PC(SO_2)$ is the estimated SO_2 concentration needed to produce doubling of SRaw in each subject. For each subject, $PC(SO_2)$ is determined by plotting change in SRaw, corrected for exercise-induced bronchoconstriction, against SO_2 concentration. The SO_2 concentration that caused a 100% increase in SRaw is determined by linear interpolation. Cumulative percentage of subjects is plotted as a function of $PC(SO_2)$, and each data point represents $PC(SO_2)$ for an individual subject. From Horstman et al (1988).

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Pulmonary function changes seen after SO_2 exposures are transient and usually resolve within 20 minutes (Koenig et al, 1981). However, many subjects with asthma in controlled studies of SO_2 exposure request bronchodilator therapy after exposure rather than waiting for the symptoms to diminish (Koenig et al, 12981; 1985; Trenga et al, In Press). Symptoms are shortness of breath, chest tightness and wheezing.

D.1.4. Inflammation. Dr Sandstrom in Sweden has published several papers showing that SO_2 exposure is associated with airway inflammation as well as PFT decrements. For instance, Sandstrom and co-workers (1989) reported inflammatory effects of SO_2 inhalation by evaluating bronchoalveolar lavage (BAL) fluid in healthy subjects. Both mast cells and monocytes were significantly elevated in BAL fluid 4 and 24 hours after exposure to 8 ppm SO_2 for 20 minutes compared to air exposure. The mast cells showed a biphasic response with elevated numbers at 4 and 24 hours but not at 8 hours post exposure. The monocytes showed a lesser but continuous elevation. Increased neutrophils were seen in nasal lavage fluid from subjects with asthma exposed to 1 ppm SO_2 (Bechtold et al, 1993). Also, Koenig and co-workers (1990) have shown, in a study of pulmonary function, that prior exposure to a sub-threshold concentration of ozone for 45 minutes (0.12 ppm) potentiates the response to a subsequent exposure to low concentrations of SO_2 (100 ppb). No significant reduction in pulmonary function was seen when an air exposure followed ozone. This result suggests that the ozone exposure altered bronchial hyperresponsiveness even though it did not alter pulmonary function. Whether the hyperresponsiveness was due to inflammatory changes was not assessed. It is generally agreed upon that airway inflammation is a more adverse effect than reversible PFTs.

D.1.5. Prevalence of SO_2 sensitive individuals. A recent report determined the prevalence of airway hyperresponsiveness to SO_2 in an adult population of 790 subjects, aged 20-44 years, as part of the European Community Respiratory Health Survey. The prevalence of SO_2 hyperresponsiveness (measured as a 20% decrease in FEV_1) in that population was 3.4%

(Nowak et al, 1997). Twenty-two percent of subjects with a methacholine positive response showed SO_2 sensitivity while only 2 out of 679 who were not methacholine positive had such sensitivity, although presence of asthma was not used directly as a risk factor. Another study screened adult subjects with asthma for SO_2 responsiveness defined as a 8% or greater drop in FEV_1 after a 10 minute challenge with 0.5 ppm SO_2 (Trenga et al, 1999). Of the 47 subjects screened, 53% had a drop in FEV_1 greater or equal to 8% (ranging from –8% to -44%). Among those 25 subjects, the mean drop in FEV_1 was -17.2%. Baseline pulmonary function indices (FEV_1 % of predicted and FEV_1/FVC%) did not predict sensitivity to SO_2. Although medication usage was inversely related to pulmonary function changes after SO_2 ($p < 0.05$), both SO_2 responders and non-responders were represented in each medication category. Total post exposure symptom scores were significantly correlated with changes in FEV_1 ($p<0.05$), FVC ($p<0.05$) and PEF ($p<0.01$) but not FEF_{25-75}.

D.2. Panel Studies

Higgins and co-workers (1995) studied a panel of 75 adult subjects with diagnoses of asthma or chronic obstructive pulmonary disease (COPD) for four weeks. Subjects recorded peak flow, symptoms, and bronchodilator use. Health outcomes were examined for associations with SO_2 and ozone using regression analysis. Sixty-two subjects completed the measurements. During the study period the maximum 24-hour levels of SO_2, ozone, and nitrogen dioxide were 45 ppb, 29 ppb, and 43 ppb respectively. Wheeze on the same day, 24 and 48 hours after exposure were significantly associated with SO_2. Dyspnea and cough were not. Bronchodilator use was significantly associated with SO_2 concentrations at 24 and 48 hour lags.

D.2.1. Mechanisms of response. In spite of all the research investigating the relationship between SO_2 exposure and responses in individuals with asthma, the mechanism of the SO_2 response is not known. At one time it appeared, from animal studies, that SO_2-induced bronchoconstriction was mediated by the vagus nerve (part of the parasympathetic branch of

the autonomic nervous system). Cooling or cutting the vagus nerve in cats abolished the SO_2 response (Nadel et al, 1965). Several therapeutic agents with varying sites of action inhibit the SO_2 response in human subjects as described later in the section on Interactions. Also atropine, which counteracts the effects of the parasympathetic nervous system, does not inhibit the SO_2 response in human subjects. Thus, there is not a clear understanding of why SO_2 elicits such a dramatic effect on the bronchial airways of subjects with asthma.

D.3. Epidemiology Studies

Epidemiologic studies in the field of air pollution health effects rely on various measures of effect. Some of the studies use anonymous data from visits to emergency departments, hospital admissions, and mortality. Epidemiologic studies also study panels of subjects who are asked to record daily lung function, symptoms, and medication use during a short time period. These data are then compared to daily air pollution concentrations.

Results from epidemiologic studies on SO_2 exposure have been consistent with findings from the controlled laboratory studies. Several epidemiology studies, using time series analysis have shown that exposure to ambient concentrations of SO_2 are associated with mortality and morbidity. Table 2 summarizes some of the epidemiologic studies on the associations between SO_2 and mortality and hospital admissions for respiratory diseases. These studies clearly demonstrate that children, the elderly and those with preexisting conditions are particularly susceptible to air pollution. It has been shown that hospital admissions for cardiovascular and respiratory illnesses have been associated with just a 4 ppb in SO_2 in Hong Kong (Wong et al, 1999). The mean SO2 concentration was 8 ppb. In Valencia, Spain, Ballester et al (1996) found an association between mortality in the elderly and those with cardiovascular disease with only a 4 ppb increase in SO_2. The mean SO_2 concentration was 15.3 ppb.

Table 2: Epidemiology studies involving SO_2 exposure and mortality and morbidity

study	city	SO2 conc	units	other pollutants	R	CI	CI	endpoint	comments
Zimirou (1998)	London	33.1 (Cool) 30.9 (Warm)	24 hr ave (ug/m3)	BS, NO2, O3	.02	.01	.03	cardiovasular mortality associated with 50 ug/m3 increase in SO2	1 hour max SO2, Paris, Lyon, Barcelona
	Paris	40.1(C) 20.1 (W)		BS, NO2, O3	.04	.01	.06	cardiovasular mortality	24 hr ave, London, Paris, Lyon, barcelona, Milan
	Lyon	76.8(C) 26.4 (W)		BS, NO2, O3	.01		.02	cardiovasular mortality	24 hr ave, Bratislava, Poznan, Lodz, Wroclaw, Krakow
	Barcelona	50.6 (C) 40.1 (W)		BS, NO2, O3	.02	.01	.03	respiratory mortality	1 hr max, Paris, Loyon, Barcelona
	Milan	248.6(C) 30.5(W)		TSP	.05	.03	.07	respiratory mortality	24 hr, Londaon, Paris, Loyon, Barcelon, Milan
	Krakow	134.8 (C) 59.5 (W)		BS	.01	.98	.04	respiratory mortality	24 hr, Poznan, Lodz, Wroclaw, Krakow
	Lodz	100.9 (C) 29.6 (W)		BS					
	Wroclaw	67.4 (C) 23.4 (W)		BS					
	Poznan	100.1 (C) 33.1 (W)		BS					
	Bratislava	103.5 (C) 83.0 (W)		TSP					
Anderson (1996)	London	32+11.7	24hr ave (ug/m3)	BS, NO2(ppb), O3 (ppb)	1.01	1.00	1.02	all cause mortality associated with increase of pollutant from 10th to 90th centile	all year, 1 day lag
					1.01	0.99	1.02	all cause	cool season, 1 day lag

study	city	SO2 conc	units	other pollutants	R	CI	CI	endpoint	comments
					1.02	1.00	1.03	all cause	warm season, 1 day lag
					1.00	0.99	1.02	cardiovascular	all year, 1 day lag
					1.00	0.98	1.02	cardiovascular	cool season, 1 day lag
					1.00	1.02	1.03	cardiovascular	warm season, 1 day lag
					1.02	0.99	1.05	respiratory mortality	
					1.02	0.98	1.06	respiratory mortality	
					1.02	0.97	1.06	respiratory mortality	
Rossi et al (1999)	Milan, Italy	124+127	daily means (ug/m3)	TSP, NO2	1.03	1.02	1.04	all cause mortality for 100 ug/m3 increase in SO2	
Kelsall et al (1997)	Philadelphi, 1974-1988	17.3+11.6	ppb	TSP, NO2, CO, O3	1.01	1.00	1.02	all cause mortality for increase in interquartile range of SO2 (single pollutant model)	
Ballester et al (1996)	Valencia, Spain	39.94+15.38	24 hr ave (ug/m3)	BS	1.00	0.99	1.02	total mortality in cold months (Nov-Apr) for 10 ug/m3 in SO2	
					1.02	1.00	1.04	total mortality warm months (May - Oct)	
					1.001	0.98	1.02	all cause >70 cold months	
					1.02	1	1.04	all cause >70 warm months	
					0.99	0.98	1.02	cardiovascular cold months	
					1.02	1.00	1.05	cardiovascular warm months	
					0.96	0.91	1.00	respiratory cold	
					1.00	0.95	1.05	respiratory warm	
Burnett et al, 1999	Toronto, Canada	5.35+5.89	ppb	PM2.5, PM10-2.5, PM10, CO, NO2, O3	1.01			hospital admissions for asthma attributable to increase of SO2 mean	
					1.02			respiratory infections	
					1.02			ischemic heart disease	
					1.00			obstructive lung disease single pollutant model	

study	city	SO2 conc	units	other pollutants	R	CI	CI	endpoint	comments
Wong et al (1999)	Hong Kong	20.2	ug/m3	NO2, O3, PM10	1.02	1.01	1.04	respiratory admission for 10ug/m3 increase in SO2	>65 years, 0 days lag
					1.01	1.00	1.02	respiratory admission for 10ug/m3 increase in SO2	overall
					1.02	1.01	1.03	cardiovascular admission for 10ug/m3 increase in SO2	>65, 0-1 day lag
					1.02	1.01	1.03	cardiovascular admission for 10ug/m3 increase in SO2	overall, 0-1 day lag
Wong et al (cont)					1.02	1.00	1.04	asthma admissions for 10 ug/m3 increase in SO2	
					1.02	1.01	1.04	COPD	
					0.99	0.98	1.00	pneumonia and influenza	
					1.04	1.01	1.06	heart failure	
					1.01	1.00	1.03	ischaemic heart disease	
					0.99	0.98	1.00	cerebrovascular diseases	
Garcia-Aymerich et al (2000)	Barcelona	46 (W) 36.4 (S); W=Oct-Mar, S= Apr-Sep	ug/m3 24 hr ave median values	BS, NO2, O3	1.04	0.91	1.19	total mortality for 50 ug/m3 increase in SO2	cohort of COPD patients
					1.04	0.85	1.28	respiratory mortality for 50 ug/m3 increase in SO2	cohort of COPD patients
					1.04	0.81	1.33	cardiovascular mortality	cohort of COPD patients
Sunyer et al (1996)	Barcelona	46 (W) 36.4 (S); W=Oct-Mar, S= Apr-Sep	ug/m3 24 hr ave median values	BS, NO2, O3	1.13	1.07	1.19	total mortality for 100 ug/m3 increase in SO2	lag 1
					1.14	1.063	1.23	respiratory mortality	lag 1
					1.13	0.99	1.28	cardiovascular mortality	lag 0
Vigotti et al (1996)	Milan	117.7	24 h ave (ug/m3)	TSP	1.12	1.03	1.23	mortality for 100 ug/m3 increase in SO2	lag 0, SO2 levels log transformed
					1.05	1	1.1	respiratory admissions for 100 ug/m3 increase	lag 0, SO2 log transformed, ages 15-64
					1.04	1	1.09	respiratory admissions for 100	lag 0, SO2 log

study	city	SO2 conc	units	other pollutants	RR	CI	CI	endpoint	comments
								ug/m3 increase	transformed, age>64
Katsouyanni et al (1997)	Athens	50	ug/m3 (median)	BS, PM10					1 day exposure
	Barcelona	45			1.029	1.023	1.035	total mortality for 50 ug/m3 increase in SO2 (Western cities)	1 day exposure
	Bratislav	13			1.008	0.993	1.024	total mortality for 50 ug/m3 increase in SO2 (Eastern cities)	1 day exposure
	Cracow	74			1.02	1.015	1.024	total mortality for 50 ug/m3 increase in SO2 (all cities)	
	Cologne	44							
	Lodz	46							
	London	29							
	Lyons	37							
	Milan	66							
	Paris	23							
	Poznan	41							
	Wroclaw	29							

RR – Relative Risk
LCI – Lower confidence interval
UCI – Upper confidence interval

Though it is difficult to separate the effects of particulate matter and SO_2 in epidemiologic studies, SO_2 has been shown to be responsible for adverse health effects, when PM had no effect. Derriennic and colleagues (1989) found that short term exposure to SO_2 was associated with respiratory mortality in people over 65 years of age in Lyons and Marseilles, and only all cause mortality in Marseilles. Particulate matter, however, had no effect on respiratory or cardiovascular mortality in the two cites. Schwartz and Dockery (1992) estimated that total mortality in Philadelphia would increase by 5% (95% CI, 3 to 7%) with each 38 ppb increase in SO_2. However, when both total suspended particulates (TSP) and SO_2 were considered simultaneously, the SO_2 association was no longer statistically significant. This was similar to the findings of Ponka et al (1998) when they modeled SO_2 and PM_{10} simultaneously in Helsinki. Masayuki et al (1986), however, implicated SO_2 as the primary source of mortality and chronic bronchitis in Yokkaichi, Japan. Masuyuki et al (1986) and associates studied the association between mortality changes from asthma and chronic bronchitis and changes in SO_2 concentrations over a 21 year period. Mortality from bronchial asthma decreased immediately after SO_2 levels decreased because of countermeasures taken against the source of air pollution and SO_2 levels met the national ambient air quality standard (maximum 1 hr concentration of 100 ppb, maximum daily average 40 ppb. Mortality due to chronic bronchitis decreased 4-5 years after the concentration of SO_2 began to meet the air standards. Although it is very difficult to use epidemiology o identify causation, in 1971 the Japanese courts accepted epidemiologic evidence showing a relationship between SDO2 and the prevalence of respiratory disease as legal proof of causation (Namekata, 1986).

Few studies have looked at the effects of air pollution on pregnancy outcomes. Recently, Wang et al (1997) looked at the association between air pollution and low birth weight in four residential areas in Beijing, China. Low birthweight is an important predictor of neonatal mortality, postnatal mortality and morbidity (McCormick, 1985). Considering both SO_2 and TSP together, Wang and colleagues found that maternal exposures to SO_2 and TSP during the third trimester of pregnancy were associated with low birth weight. The adjusted odds ratio was 1.11 (95% CI, 1.06-

1.16) for each 38 ppb increase in SO_2 and 1.10 (95% CI, 1.05-1.14) for each 100 ug/m^3 increase in TSP. Adjusting for maternal age and other covariates, this study estimated a 7.3 g and 6.9 g reduction in birth weight for a 38 ppb increase in SO_2 and 100 ug/m3 increase in TSP. More recently, Rogers et al (2000) studied the association between low birth weight and exposure to SO_2 and TSP in Georgia, USA. This study found that exposure to TSP and SO_2 above the 95th percent (22 ppb) yielded an adjusted odds ratio of 1.27 (95% CI= 1.16-7.13). Xu and colleagues (1995) found that SO_2 and TSP were also associated with preterm delivery in Beijing, China. In the study area, the average SO2 concentration was 38 ppb, maximum 240 ppb. The estimated reduced duration of gestation was .075 week for each 38 ppb increased in SO_2. Using logistic regression, the estimated odds ratio for preterm delivery was 1.21(CI=1.01-1.46) for each ln ug/m^3 increase in SO_2 and 1.10 (95%CI=1.01-1.20) for each 100 ug/m^3 increase in TSP (ln ug/m^3 is the form used by the authors). Since children and asthmatics are particularly sensitive to the effects of air pollution several studies have focused on the respiratory effects of ambient air pollution on this susceptible population. Buchdahl et al (1996) estimated that the incidence of acute wheezing in children would increase by 12% with each standard deviation in SO_2 level in West London. The hourly average concentration of SO_2 was 8 $\pm$ 5 ppb for all seasons.. Timonen and Pekkanen (1997) studied the effects of air pollution on the respiratory health of children 7 to 12 years of age in Kuopio, Finland. This study found an association between SO_2 and PEF and incidence of upper respiratory symptoms in non-asthmatic children with coughing symptoms. Infectious airway diseases (except pneumonia) and irritations of the airways were shown to be associated with SO_2 in East Germany (Kramer et al, 1999). Both SO_2 and TSP were included in the regression model simultaneously. This study showed that the decrease in SO_2 and TSP levels in East Germany since 1991had a favorable effect on these diseases. Schwartz et al (1995) studied the acute effects of summer air pollution on respiratory symptoms in children in six U.S. cities. They found that sulfur dioxide was associated with incidences of cough and lower respiratory symptoms, using a single pollutant model. These findings, however, could be confounded by PM_{10}. Segala et al (1998) found a strong

association between short-term exposure to SO_2 and the risk of asthma attack in children in Paris. The odds ratio for an asthma attack was 2.86 for an increase of 18.9 ppb of SO_2 on the same day. In Singapore, Chew et al (1999) found that asthmatic children were sensitive to ambient levels of SO_2 and TSP that were within acceptable ranges. They reported an increase of 2.9 visits to the emergency room for every 7.6 ppb increase in atmospheric SO_2, lagged by 1 day on days when levels were above 26 ppb.

E. Children vs. Adults

Physiologic and respiratory differences between adults and children contribute to the increased sensitivity of children to air pollutants. Children have a higher alveolar surface area to body mass ratio compared to adults resulting in a larger air-tissue gas exchange area. Compared to adults the respiration rate of an infant is 40 breaths/min compared to 15 breaths/min for an adult (Snodgrass, in Similarities and Differences between Children and Adults: Implications for Risk Assessment). The higher inhalation rate in children would result in an increased uptake of an inhaled pollutant. Table 3 compares the inhalation rates of children and adults (Exposure Factors Handbook, 1997).

Table 3: Inhalation rates of children and adults

Children (<1 year)	4.5 m^3/day (average)
Children (1-12 years)	8.7 m^3/day (average)
Adult female	11.3 m^3/day (average)
Adult male	15.2 m^3/day (average)

Inhalation rates are affected by age, gender, weight, health status and level of physical activity (Exposure Factors Handbook, 1997). Linn et al (1992) conducted a study on the inhalation rates of healthy and asthmatic adults and children in the Los Angeles Area. This study reported that healthy adults (n=20) had an average ventilation rate of 0.78 m^3/hr, elementary school students (n=17) an average rate of 0.90 m^3/hr and high school students (n=19) a rate of 0.84 m^3/hr. Asthmatics were found to have higher breathing rates. Elementary and high school children with asthma (n=13) had the highest ventilation rate - 1.20 m^3/hr, whereas adult asthmatics (n=49) had

an average ventilation rate of 1.02 m^3/hr. Layton (1993) calculated breathing rates based on oxygen consumption and reported that male children between 15-18 had the highest daily ventilation rate (17 m^3/day), females 9-11 had an inhalation rate of 13 m^3/day and children 6-8 had a daily inhalation rate of 10 m^3/day. (The description of the Linn data came from Ch 5 in the Exposure Factors handbook sent to us by Dr Lipsett. The citation for the article is the Proceedings of the Second EPA/AWMA Conference on Troposphereic Ozone, 1991 ppf 701-712).

The health risk associated with air pollutants is a function of air concentration, duration and frequency of exposure as well as inhalation rate. Air pollutant concentrations vary at different locations: work, school, home, outdoors. Exposure levels, therefore, depend on the amount of time spent in various locations. According to the 1997 Exposures Factors Handbook, children (ages 3-11) spend 5 hr/day (weekdays) and 7 hr/day (weekends) outdoors compared to adults who only spend 1.5 hr/day outdoors. The increased time spent outdoors predisposes children to the effects of inhaled pollutants.

The toxic effects of a pollutant depend, in part, on the frequency and duration of exposure. For outdoor pollutants, such as SO_2, the amount of time spent outdoors contributes to the dose of the toxicant. The California Children's Activity Survey (1991) was designed to estimate the time children less than 12 years of age spent in various locations and doing various activities on a typical day. The activities that were focused on were those that would likely result in significant exposure to air pollutants. Children (n=1200) from various regions of California, Southern Coast, San Francisco Bay Area, and the rest of the state completed the survey. This study reported that children spent three times as much time as adults playing sports and other vigorous activities and more than 15 times as much time in simple play activities than adults. The time children spent outdoors each day was also more than twice that of adults, 141 minutes vs. 73 minutes respectively.

F. Sensitive sub-populations

People with asthma are particularly sensitive to the effects of SO_2. Asthma is a lung disease characterized by airway obstruction, airway inflammation and increased airway responsiveness to a variety of stimuli. As of 2000, over 18 million people or 7 % of the U.S. population were estimated to have asthma. Some estimates find that 18% of children have asthma. Although death resulting from asthma is rare, hospitalization from asthma does occur regularly. Weitzman et al (1992) reported that 10% of children in the U.S. (<18 years of age) with asthma were hospitalized within the past year. It has been estimated that asthma is responsible for 27 million patient visits, 134,000 hospital admissions, 6 million lost work days and 90 million days of restricted activity. Asthma is the most common chronic illness of childhood and the primary cause of school absences. Asthma also is a multi-factorial illness with a wide range of individual susceptibilities and sensitivities. The U.S. EPA in the Second Addendum reviewed studies from 1982 to 1986 pertaining to the respiratory effects of SO_2 exposure and supported the conclusion that asthmatic subjects are more sensitive to SO_2 than are non-asthmatic individuals. Several of the studies reviewed by the U.S. EPA (1986) also showed evidence that asthmatics undergoing moderate to heavy exercise suffered from bronchoconstriction after exposure to 0.5 ppm SO_2. These studies found that bronchoconstriction can result in just 5 to 10 minutes of exposure.

Since 1986 the U.S. EPA published the supplement to the Second Addendum of the criteria document for sulfur oxides (US EPA, 1994) assessing new studies which focused on the effects of SO_2 on asthmatics. Included in this review was a study by Horstman et al (1986). The aim of this study was determine the shortest duration of SO_2 exposure necessary to induce bronchoconstriction in asthmatics. Horstman et al (1988) reported that asthmatic subjects undergoing moderate exercise (minute ventilation = 40 L/min) experienced broncoconstriction after 2 and 5 minute exposures to 1.0 ppm SO_2. Balmes et al (1987) reported bronchoconstriction in asthmatics after 1 minute of 1.0 ppm SO_2 during eucapnic hyperpnea (60 L/min). Table 4 summarizes the findings by Balmes et al. Two of the 8 subjects developed large increases in SRaw

and chest tightness after inhalation of 1.0 ppm for 1 minute and seven of the 8 asthmatic subjects developed wheezing, chest tightness or dyspnea and requested inhaled brochodilator therapy after 0.5 ppm SO_2 for 3 and 5 minutes.

Table 4: Average increases in SRaw resulting from exposure to 0.5 or 1.0 ppm SO_2 for various time periods (Adapted from Balmes et al, 1987)

SO_2 Concentration (ppm)	Duration of exposure (minute)	SRaw (L $\times$ cm H_2O/L/s)	% increase SRaw above baseline
0.5	1	25 ± 0.3	34
0.5	3	13±3.2	173
0.5	5	19.6 ± 4	234
1.0	1	7.5 ± 4.7	93
1.0	3	31.4 ± 7.4	395
1.0	5	44.1 ± 9.8	580

The above studies clearly demonstrate the increased susceptibility of asthmatics to the adverse effects of low concentrations of SO_2. In fact, asthmatics undergoing moderate to heavy exercise are even more susceptible to these adverse health effects.

Those with chronic obstructive pulmonary disease (COPD) may also be highly susceptible to the effects of SO_2. Anderson et al (1997) reported that the association between 24 hr SO_2 concentrations and hospital admissions for COPD in a meta-analysis of 6 European cities was significant in the warm season (RR=1.05, 95% CI=1.01-1.10).

G. Conclusion

In general the studies assessed in this review indicate that children and people with asthma are particularly susceptible to the effects of SO_2, even at concentrations and durations below the current California one-hour standard of 0.250 ppm. It has been clearly demonstrated that exercise exacerbates the adverse responses experienced by this sub-population. Exercising asthmatics can suffer from bronchoconstriction within minutes after exposure to SO_2 at levels of 0.25 ppm (Horstman et al, 1986; 1988). Koenig et al (1981) reported significantly greater pulmonary function decrements in a group of children with asthma exposed to 1.0 ppm during moderate exercise than in a similar group exposed at rest (Koenig et al, 1980). There is one report of decrements after 0.1

ppm SO_2 exposures (Trenga et al, In Press). Studies have also shown that children are more susceptible to outdoor air pollutants than normal, healthy adults. This may be due to the physiologic differences between adults and children as well as the increased time that children spend outdoors engaging in physical activities. Also, as shown in Table 2, epidemiologic studies have seen adverse health effects at short-term exposures to SO_2 in the range at concentrations as low as 5 ppb. Zimirou (1998) reported cardiovascular mortality at one-hour maximum values of 10 – 19 ppb. As listed in Table 2, several studies see increased mortality with a 38 ppb increase in SO_2. It appears that a one-hour standard of 0.250 ppm (such as currently in effect in California) will not protect all members of the community.

H. References

Anderson HR, Ponce de Leon A, Bland JM, Bower IS, Strachan DP. Air pollution and daily mortality in London: 1987-92. BMJ 1996; 312:665-669.

Ballester F, Corella D, Peres-Hoyos S, Hervas A. Air pollution and mortality in Valencia, Spain: a study using the APHEA methodology. J Epidemiol Community Health 1996; 50:527-533.

Balmes JR, Fine JM, Sheppard D. Symptomatic Bronchoconstriction after short-term inhalation of sulfur dioxide. Am Rev Resp Dis 1987; 136:1117-1121

Bechtold WE, Waide JJ, Sandstrom T, Stjenberg, N, McBride D, Koenig, J. Chang IY, Henderson RE. Biological markers of exposure to SO~: S-sulfonates in nasal lavage. J Expo Analy Environ Epidemiol 1993; 3:371-382.

Bethel RA, Boushey HA, et al. Effect of exercise rate and route of inhalation on sulfur dioxide bronchoconstriction in asthmatic subjects. Am Rev Respir Dis 1983; 128:
592-596.

Bethel RA, Sheppard ID, Epstien J. Interaction of sulfur dioxide and dry cold air in causing bronchoconstriction in asthmatic subjects. J Appl Physiol 1984; 57:
491-423.

Buchdahl R, Parker A, Stebbings T, Babiker, A. Association between air pollution and acute childhood wheezy episodes: prospective observational study. BMJ 1996; 312:661-665.

Chew FT, Goh DYT, Ooi BC, Saharom R, Hui JKS, Lee BW. Association of ambient air pollution levels with acute asthma exacerbation among children in Singapore. Allergy 1999; 54:320-329.

Costa DL, Amdur MO. Air Pollution IN: Klaassen CD (ed) Casarett & Doull's Toxicology: the basic science of poisons, Fifth Edition McGraw Hill, New York, 1996.

Derriennec F, Richardson S, Mollie A, Lellouch J. Short-term effects of sulphur dioxide pollution on mortality in French cities. Int J Epidemiol 1989; 18:186-197.

EPA. Supplement to the Second Addendum (1986) to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982): Assessment of new findings on sulfur dioxide acute exposure health effects in asthmatic individuals. EPA-600R-93/002: August 1994.

EPA. Review of the National Ambient Air Quality Standards for Sulfur Oxides: Assessment of Scientific and Technical Information. EPA-452R-94-013: September 1994.

Exposure Factors Handbook: August 1997.

Frank NR, Amdur MO, Worcester J, Whittenberger JL. Effects of acute controlled exposure to SO_2 on respiratory mechanics in healthy male adults. J Appl Physiol 1962; 17:272-258.

Horstman DH, Seal E, Folinsbee, LJ, Ives P, Roger LJ. The relationship between exposure duration and sulfur dioxide inducted bronchoconstriction in asthmatic subjects. Am Ind Hyg Assoc J 1988; 49:38-47.

Horstman DH, Folinsbee LJ. Sulfur dioxide-induced bronchoconstriction in asthmatics exposed for short durations under controlled conditions: A selected review. IN: Utell MJ, Frank R. Susceptibility to inhaled pollutants. ASTM, Philadelphia, 1986.

Kelsall JE, Sarnet JM, Zeger SL, Ku J. Air pollution and mortality in Philadelphia, 1974- 1988. Am J Epidemiol 1997; 146:750-762.

Kirkpatrick MB, Sheppard ID, Nadel JA, Boushey HA. Effect of oronasal breathing route on sulfur-dioxide induced bronchoconstriction in exercising asthmatic subjects. AmRevRespIDisl982; 125: 627-631.

Koenig JQ, Pierson WE, Frank R. Acute effects of inhaled S02 plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. Environ Res 1980; 22: 145-153.

Koenig JQ, Pierson WE, Horike M, Frank R. Effects of 502 plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. Environ Res 1981; 25:340-348.

Koenig JQ, Morgan MS, Horike M, Pierson WE. The effects of sulfur oxides on nasal and lung function in adolescents with extrinsic asthma. J Allergy Clin Immunol 1985; 76: 813-818.

Koenig JQ, Covert DS, Hanley Q, van Belle G, Pierson WE. Prior exposure to ozone potentiates subsequent response to sulfur dioxide in adolescent asthmatic subjects. Am Rev Respir Dis 1990; 141: 377-380.

Koenig JQ. Atmospheric pollutants: Sulfur dioxide and particulate matter. IN: Asthma. Eds. Barnes PJ, Grunstein MM, Leff AR, Woolcock A]. Lippincott-Raven, Philadelphia, 1997; 1151-1156

Kramer U, Behrendt H, Dolgner R, Ranft U, Ring J, Willer H, Schlipkoter HW. Airway diseases and allergies in East and West German children during the first five years after reunification: time trends and the impact of sulphur dioxide and total suspended particles. Int J Epidemiol 1999; 28:865-873.

Layton DW. Metabolically consistent breathing rates for use in dose assessments. Health Phys 1993; 64:23-36.

Linn WS, Shamoo DA, Spier CE, Valencia LM, Anzar, UT, Venet, TG, Hackney JD. Respiratory of 0.75 ppm sulfur dioxide in exercising asthmatics: influence of upper-respiratory defenses. Environ Res 1983; 30:340-348.

Linn WS, Shamoo DA, Venet TG, Bailey PM. Comparative effects of sulfur dioxide exposures at 5 C and 25 C in exercising asthmatics. Am Rev Respir Dis 1984; 129:234-239.

Linn WA, Shamoo DA, Venet TG, Spier CF. Combined effects of sulfur dioxide and cold in exercising asthmatics. Arch Environ Health 1984; 39:339-345.

Masayuki I, Yoshida K, Masayoshi K. Mortality from asthma and chronic bronchitis associated with changes in sulfur oxides air pollution. Arch Environ Health 1986: 41: 29-35.

McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985; 312:82-90.

Nadel IA, Salem H, Tamplin B, Tokowa Y. Mechanism of bronchoconstriction during inhalation of sulfur dioxide. J App] Physiol 1965; 20:164-167.

Namekata T. The Japanese compensation system for respiratory disease patients: background, status and trend, and review of epidemiological basis. In Lee, Schneider, Grant, and Verkerk (eds). Aerosols. Lewis Publishers, Chelsea MI, 1986.

Nowak D, Jorres R, Berger J, Claussen M, Magnussen H, Airway responsiveness to sulfur dioxide in an adult population sample. Am J Respir Crit Care Med 1997; 156: 1151-1156.

Ponka A, Savela M, Virtanen M. Mortality and air pollution in Helsinki. Arch Environ Health 1998; 53: 281-286.

Rogers JF, Thompson SJ, Addy CL, McKeown RE, Cowen DJ, Decoufle P. Association of very low birth weight with exposures to environmental sulfur dioxide and total suspended particulates. Am J Epidemiol 2000; 151:602-613..

Sandstrom T, Stjernberg N, Andersson M-C, Kolomodifl-Hedman B, Lundgren R, Rosnehall L, Angstrom T. Cell response in bronchoalveolar lavage fluid after exposure to sulfur dioxide: A time response study. Am Rev Respir Dis 1989; 140: 1828-1831.

Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 1992; 145:600-604.

SchwartzJ, Dockery DW, Neas LM, Wypij D, Ware JH, Spengler J, Koutrakis P, Speizer FE, Ferris BG. Acute effects of summer air pollution on respiratory symptom reporting in children. AmJ Respir Crit Care Med 1994; 150:1234-1242.

Segala C, Fauroux B, Just J, Pascual L, Grinfeld A, Neukirch F. Short-term effect of winter air pollution on respiratory health of asthmatic children in Paris. Eur Respir J 1998; 11:677-685.

Sheppard D, Wong WS, Vehara CF, Nadel JA, Boushey, HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. Am Rev Respir Dis 1980; 122:873-878.

Sheppard ID, Salsho A, Nadel JA, Boushey HA. Exercise increases sulfur dioxide induced bronchoconstriction in asthmatic subjects. Am Rev Respir Dis 1981; 123:486-491.

Snodgrass, WR. Physiological and biochemical differences between children and adults and determinants of toxic response to environmental pollutants. IN: Guzlean PS, Henry CJ, Olin SS. Similarities and differences between children and adults: implications for risk assessment. 1151 Press, Washington DC: (year?)

Speizer FE, Frank R. The uptake and release of S02 by the human nose. Arch Environ Health 1966; 12:725-758.

Sunyer J, Castellsague J Saez M, Tobias A, Anto JM. Air pollution and mortality in Barcelona. 1 Epidemiol Comm Health 1996; 50 (Suppl 1): 576-580.

Trenga CA, Koenig JQ, Williams PV. Sulphur dioxide sensitivity and plasma antioxidants in adult subjects with asthma. Occup Environ Med 1999; 56: 544-547.

Trenga CA, Koenig JQ, Williams PV. Dietary antioxidants and ozone-induced bronchial hyperresponsiveness in adults with asthma. Arch Environ Health (In Press)

Timonen KL, Pekkanen J. Air pollution and respiratory health among children with asthmatic or cough symptoms. Am J Respir Crit Care Med 1997; 156:546-552.

Ung N, Koenig JQ, Shaprio GG, Shapiro PA. A quantitative assessment of respiratory pattern and its effect on dentofacial development. Am J Orthod Dentofac Ortho 1990; 98: 523-532.

Viggotti MA, Rossi G, Bisanti L, Zanobetti A, Schwartz J. Short term effects of urban air pollution on respiratory health in Milan, Italy, 1980-89. J Epidemiol Comm Health 1996; 50 (Suppl 1): 571-575.

Wang X, Ding H, Ryan L, Xu X. Association between air pollution and low birth weight: A community-based study. Environ Health Perspect 1997; 107: 514-520.

Wiley JA, Robinson JP, Cheng YT, Piazza T, Stork L, Pladsen K. Study of Children's Activity Patterns. Final Report Contract No. A733-149; Survey Research Center: University of California, Berkeley: September 1991.

Wong TW, Lau TS, Yu ST, Neller A, Wong SL, Tam W, Pang SW. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occup Environ Med 1999; 56:679-683.

Xu X, Ding H, Wang X. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study. Arch Environ Health 1995; 50: 407~15.

Zmirou D, SchwartzJ, Saez M, Sanobetti A, Wojtyniak B, Touloumi G, Spix C, Ponce de Leon A, Le Moullec Y, Bacharova L, Schouten J, Ponka A, Katsouyanni K. Time-series analysis of air pollution and cause-specific mortality. Epidemiology 1998; 9:495-503.